UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,115	05/05/2001	Emil V. Kozarov	UF-10380	9072

20306 7590 05/28/2004

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,115	KOZAROV ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-13 and 17-29* is/are pending in the application.

4a) Of the above claim(s) *6-10 and 17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Kozarov *et al.*

Date of priority: 05/05/2001

Response to Amendment

The Amendment filed 03/04/2004 in response to the Office Action of 10/31/2003 is acknowledged and has been entered.

Claims 1-2 and 11-13 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 1-2 and 11-13 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and for the reasons set forth below.

Applicants have argued (Response, page 8) and presented evidence (Kozarov Declaration) of an in-vitro VEGF proliferation model demonstrating the inhibition of angiogenesis via *gingipain* preparations. Applicants further argue (Response, page 9) that such evidence is a correlating model for antiangiogenic compunds such as the *P. gingivalis* cysteine

proteases. Applicants have further argued that the declaration of Dr. Kozarove provides **in vivo** evidence of the enablement of the claimed method wherein paragraphs 8-11 of the Declaration describe the effect of *P. gingivalis* cysteine proteases on lung and breast cancer murine animal models.

These arguments and Applicant's Declaration have been carefully considered but are not found persuasive. Although applicants have presented a correlation between the anti-angiogenic effects of certain compounds in-vitro to their anti-cancer effects in-vivo, it cannot be predicted that the **claimed** compounds would function in the same manner as presented in Applicant's declaration. The claimed compounds to be used in the method are selected from the group consisting of discrete cysteine protease polypeptides: PrtP, HagA, HArep1, Harep2, HArep3, HArep4- all of which are derived from *Porphyromonas gingivalis*.

In contrast, the data presented in the declaration is based on a completely distinct pharmaceutical composition. For example, paragraph 8 of the declaration notes that "the purified gingipain preparation, as described above, was administered intratumorally (IT) to lung and breast cancer models". "Above", in this sense, appears to be based on the gingipain preparation used in the in-vitro experiments. Along these lines, the declaration further teaches (page 3, line 6) that the enzymes in this experiment were purified gingipains: gingipain R (which appears to be a complex of RgpA and RgpB) and gingipain K. Here, it should be noted that neither RgpA, RgpB, nor gingipain K appears in the claimed method. The declaration further teaches (page 2) that RgpA and RgpB are arginine-specific cysteine proteases and that Kgp is a lysine-specific cysteine protease. Thus, it appears that applicants used a *complex* of proteases which includes "*P. gingivalis* W83 lysine-specific and arginine-specific cysteine protease-enriched SPF (soluble

protein fraction) in their experiments. However, there is no evidence that the proteins used in the experiments are the same as the cysteine proteases used in the claimed method nor is there any evidence that a complex preparation (more than one protease) would provide the same type of biological activity as one protease used alone. Applicants only state that these proteases share homology and that HA2 (HArep2) is a subunit of both HagA and RgpA. However, applicants do not specifically teach what percent homology is shared (10%, 20%, 50% ?) between the proteases presented in the declaration compared to the proteases used in the claimed method nor do applicant's present any evidence that HArep2, used alone, would predictably invoke an antiangiogenic response. Those of skill in the art recognize that amino acid sequence homology, alone, does not specifically define nor impart biological function to a particular polypeptide. This is, in part, due to the chemical nature of the amino acids themselves, which give rise to the three-dimensional arrangement of the polypeptide. For example, Bowie *et al.* (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative

substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are further exemplified by Burgess *et al.* (J.of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and *biological activity* of the protein and by Lazar *et al.* (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, because the compounds presented in applicant's declaration are substantially different in structure and number from those used in the claimed method, it is maintained that one of skill in the art would not be enabled to practice the claimed method without undue experimentation. Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

May 27, 2004

GARY NICKOL
PRIMARY EXAMINER